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STUDY OF FEBRILE NEUTROPENIA DURING THE INDUCTION PHASE OF CHILDHOOD ALL : A SINGLE CENTER EXPERIENCE

Dr Gokul R Pillai* Senior Resident, Department of Paediatric Oncology, Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar, Maharashtra, India. *Corresponding Author

Dr Aditi Lingayat Professor and Head, Department of Paediatric Oncology, Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.

Dr Farookh Aziz Associate Professor, Department of Paediatric Oncology, Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.

Dr Suyog Nagare Assistant Professor, Department of Paediatric Oncology, Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.

ABSTRACT

Introduction: Febrile neutropenia is a dreaded complication in the treatment of acute leukemia in children. This medical emergency is more common in the intensive chemotherapy phases. ***Objectives:*** In this study, we aimed to determine the epidemiological, clinical, and microbiological characteristics of such episodes in pediatric patients with acute leukemia started on induction chemotherapy. ***Materials And Methods:*** Seventy two episodes of febrile neutropenia in 63 children (34 females and 29 males) were included in the study. All of the episodes were treated at a tertiary cancer center of Maharashtra, India from January 1, 2023 to December 31, 2024. ***Results:*** The febrile neutropenia episodes had an equal gender predilection with a mean age of 6.8 ± 3.7 years. B-acute lymphoblastic leukemia (79.1%) was the most common phenotype and high risk was the most common risk group. The upper respiratory tract was the most common focus (34.7%) identified. The mean duration of the episodes was 5.7 ± 3.9 days. The mean absolute neutrophil count was 259 ± 150 per mm^3 and 19.4% of cases had profound neutropenia. We found that 41.7% of episodes had culture positivity with Methicillin-Resistant *Staphylococcus aureus* (MRSA) as the most common organism isolated. The mean antibiotic duration was 11.5 +/- 5.0 days—with aminoglycosides being used in two-thirds of the episodes. Antifungals were used in 29.2% of episodes. Patients survived in 91.7% of the episodes, with sepsis the leading cause of mortality in 50% of cases. ***Conclusions:*** Key drivers for the decrement of febrile neutropenia-related morbidity and mortality include proper precautions, close monitoring, risk factor identification, the rapid empirical use of antibiotics, and the timely modification of treatment.

INTRODUCTION

Acute leukemia is the most common group of malignancies in children with high cure rates approaching 90%.[1] However, the outcomes are often marred by treatment-related complications - the most significant of them being febrile neutropenia (FN), which results from bone marrow suppression. It is a medical emergency and time to antibiotic administration is a key factor, especially in high-risk patients.[2] Approximately, 80% of the patients undergoing chemotherapy for hematological malignancies experience at least one episode of FN, and there is an increased risk of prolonged FN.[3] Induction phase of chemotherapy is the most intensive phase of the treatment, with increased risk of FN and mortality. Hence, we planned this study to see the epidemiological profile of FN during induction chemotherapy and to derive inferences on the most common microbial agents implicated.

MATERIALS AND METHODS

This prospective study was conducted between January 1, 2023 and December 31, 2024 at the Department of Pediatric Oncology, Government Medical College and Cancer Hospital, Chhatrapati Sambhajinagar, Maharashtra, India. It included all patients with acute leukemia under 14 years of age i.e. 63, who had febrile neutropenia during their induction chemotherapy. Febrile neutropenia was defined as per Infectious Diseases Society of America (IDSA) guidelines and was defined as fever>101°F or >100.4°F (for >1 hour) with an Absolute Neutrophil Count (ANC) <500/mm^3 or <1000/mm^3 with an expected fall in the next 48 hours. ANC<100/mm^3 was defined as profound neutropenia.[4] Non-infectious causes of fever were excluded. All the included patients underwent a detailed history and meticulous clinical examination, including identification of possible fever foci.Laboratory investigations for all patients included complete blood count (CBC) with absolute neutrophil count (ANC), peripheral smear, liver function test, and renal function test. Culture and sensitivity of blood and urine were sent for all patients and other samples as per clinical discretion. Chest skiagram and investigations were tailored for each patient. Risk stratification was done based on the protocol used. For B-Acute Lymphoblastic Leukemia (B-ALL) and T-ALL, initially-modified BFM-90 protocol was used which was followed by BFM-09 and ICiCLeALL-14 ver3.0 (Indian Childhood Collaborative Leukemia Group) protocols. For the relapsed ALL cases, the UK-ALL-R3 protocol and for Acute Promyelocytic Leukemia (APML) cases, the APML4 protocol was used.

All patients were started on broad-spectrum antibiotics, awaiting the culture reports. The initial empirical antibiotic was either an antipseudomonal beta-lactam, third/fourth generation cephalosporin, or a carbapenem in all high-risk patients. A second anti-gram negative agent or a glycopeptide was reserved for clinically unstable patients or when resistant infection was suspected. Initial or step-down outpatient management was tried in low-risk patients. If the patient was improving with the above regimen, they were continued or shifted to monotherapy (after 24-72 hours) if no microbiological contraindications. Antibiotic modification for fever persistence also depended on the culture reports. In high-risk patients, antibiotics were discontinued if blood cultures were sterile at 48 hours if the patient was afebrile with evidence of marrow recovery. In low-risk patients, antibiotics were discontinued if the patient was afebrile and the blood culture was sterile at 48 hours. In Invasive Fungal Disease

(IFD) high-risk patients, either liposomal amphotericin B or caspofungin was added if the fever was persistent for >96 hours. Chemotherapy was skipped only in life-threatening episodes.

Statistical Analysis

Microsoft Excel 2021 was used to collect and process data. Nominal and ordinal values are presented as frequencies (n) and proportions (%) and numerical values as average values and standard deviations.

RESULTS

Seventy two separate episodes of febrile neutropenia were documented in 63 patients over the study period of 2 years. All of them had been started on induction chemotherapy for acute leukemia. Patient demographics have been detailed in Table 1.

Unfavorable cytogenetics accounted for 15% of high-risk ALL cases. Anthropometric data revealed mean height of 110.4 ± 21.8 cm, mean weight of 18.4 ± 7.5 kg and mean BMI of 14.4 ± 1.2 kg/m^2. 18.1% of episodes occurred in malnourished children. The mean maximum fever recorded was 103 ± 0.8°F, with a mean duration of 5.7 ± 3.9 days. The mean time to antibiotic administration since fever onset was 6.16 ± 5.4 hours. 95.8% of cases had a documented source of infection - with 34.7% of cases contributed by upper respiratory tract infection. (Table 2) The mean ANC was 259 +/- 150 per mm^3, and 19.4% of the cases had profound neutropenia. (Table 3) All the patients had cultures of blood and urine sent. Pus cultures were sent in 13.9% and CSF in 4.2% of cases. 41.7% had culture positivity, predominated by Gram-positive organisms - with Methicillin-Resistant *Staphylococcus aureus* (MRSA) the most common organism isolated, followed by *Pseudomonas aeruginosa*. (Table 3) Antibiotics were used in all patients, with a mean duration of 11.5 +/- 5.0 days - with aminoglycosides being used in two- thirds of the episodes. Antifungals were used in 29.2% of episodes. Chemotherapy was skipped in 12.5% of cases. 26.4% of episodes needed at least some form of blood component transfusion. Most of the cases were uncomplicated, with 8.3% having shock, 4.2% having disseminated intravascular coagulation, and 2.8% having intracranial hemorrhage. Patients survived in 91.7% of the episodes, with the leading cause of mortality being sepsis - in 50% of death cases.

DISCUSSION

Acute leukemia is the most common pediatric malignancy, with a slight male predominance and peak diagnosis between 3 and 6 years of age.[5] The mean age of our cohort was 6.8 ± 3.7 years, with an equal gender predilection. The age incidence was similar to those observed in the earlier studies in the pediatric cohort.[6,7] In the ALL stratification into SR, IR, and HR groups, our study showed most of the episodes in the HR groups, although the overall leukemia cohort mostly consists of IR cases.[6] This was expected due to the tertiary care nature of the institute, and the more intensive induction regimen in the HR cohort, leading to a higher risk of FN. Relapses were treated with the UK-ALL-R3 protocol and APML with the APML4 protocol. However, there was a variance in the treatment of ALL cases, with the earlier cases being treated as per modified BFM-90 protocol, and later by BFM-09 and ICiCLeALL-14 ver3.0 protocols.

Children with acute leukemia are at risk of bacterial, viral, fungal, and parasitic infections.[8] The different factors implicated in this increased predisposition are disruptions in mucocutaneous integrity, defects in adaptive immunity, disruptions in normal bacterial flora, functional asplenia, and nutritional and neurogenic factors.[9] Fever may also be due to manifestations of the disease process, chemotherapy medications, and reactions to blood products - and such cases were excluded from our study. In children, the spectrum of oncological diagnosis and chemotherapeutic regimen (therapeutic in many cases in contrast to palliative) is different than in adults - accounting for the difference in the manifestations of FN in these age groups. In children, there is a higher rate of fever without a defined focus, and when defined - the source is most likely upper respiratory. Our study, however, had an identified focus in most of the cases - with upper respiratory tract infections predominating, similar to the literature.

The mean time to antibiotic administration since fever onset in our study was 6.16 ± 5.4 hours. The number is slightly skewed due to the delayed presentation of some of the outpatients, although the inpatients initiated antibiotics in the golden interval. Time to antibiotic administration is highly significant in high risk patients, although in low risk patients remains a conundrum.[10] The mean ANC was 259 ± 150/mm^3, with profound neutropenia observed in 19.4% of the cases. ANC nadir is an important prognostic factor in the outcome of FN. In our study, 42.8% of profound neutropenia cases succumbed and none of the mortality occurred without profound neutropenia.

Laboratory-documented infections occur in only 20%–30% of FN episodes.[11] Our study showed slightly higher figures with culture positivity in 41.7% of patients. Blood and urine samples for culture and sensitivity have to be obtained in all patients, and other samples according to the clinical suspicion. Our study strictly adhered to this dictum, may be contributing to the increased detection. There has been an increased incidence of infection by Gram-positive organisms as well as resistant Gram-negative organisms over the past decades.[9] Gram-positive organisms slightly predominated in our culture reports - with MRSA being the most common.

Pseudomonas aeruginosa was the most common Gram-negative organism. This was similar to some studies[7] while different from an earlier Indian study, which showed more positivity for Gram-negative isolates. Regarding antibiotic therapy, the current recommendations favor monotherapy over combination therapy, with the agents preferred for monotherapy either an antipseudomonal beta-lactam, fourth-generation cephalosporin, or carbapenem. A second-line Gram-negative agent or glycopeptide is added when a resistant infection is suspected or if the patient is hemodynamically unstable. The duration and change of antibiotics are determined by the culture results and the risk assessment of FN.[12] In our cohort, antibiotics were used in all patients, with a mean duration of 11.5 +/- 5.0 days - with aminoglycosides being used in two- thirds of the episodes. The other common antibiotics were penicillins (40.3%), carbapenem (31.9%), and cephalosporins (30.6%). Antibiotic upgradation was done in 61.1% (n=44) of our cohort, either due to fever persistence, culture reports, or patient's condition. Although we tried to be stringent to the international guidelines, such a strict policy couldn't be adhered to in most of the cases due to outside treatment, prior use of antibiotics, and institutional guidelines (based on culture reports). Antifungal therapy is initiated if fever is persistent in FN which are at high risk of Invasive Fungal Disease.[12] Antifungals were used in 29.2% of episodes. None of the patients developed Invasive Fungal Disease.

Chemotherapy was skipped in 12.5% of cases. Although our study showed an increased incidence of mortality in such episodes, the results may be biased due to the performance of such intervention in cases who already had a life-threatening episode. Most of the cases were uncomplicated, with 8.3% having shock, 4.2% having disseminated intravascular coagulation, and 2.8% having intracranial hemorrhage.

Patients survived in 91.7% of the episodes, with the leading focus of mortality being sepsis - in 50% of deaths. The mortality was slightly higher than the published literature,

which reports it to be around 7.5%.[6] Some of the potential contributors include the delayed presentation and the greater proportion of profound neutropenia in the cohort.

CONCLUSION

Although the prognosis of acute leukemia is constantly improving with treatment advancements, the treatment-related complications, especially febrile neutropenia remain a significant concern. The cornerstones for reducing infection-related morbidity and mortality include infection prevention, adequate parental counselling of warning symptoms, close monitoring, timely use of antibiotics and their timely upgradation. Apart from this, culture isolation of organisms is paramount, as it helps devise new treatment algorithms and the timely diagnosis of new resistant organisms. Although there exists specific guidelines for the management of febrile leukemia in this patient cohort, sometimes it is often sidelined due to the different institutional policies and the different organisms isolated (and their resistance patterns) in different geographical areas.

Table 1 Patient Characteristics

Age (years)	Mean: 6.8 ± 3.7	Median: 6.5 (1-14)
Gender		
Male	36	50%
Female	36	50%
Diagnosis		
B-ALL	57	79.1%
T-ALL	12	16.7%
APML	3	4.2%
Newly diagnosed		
Relapse	67	93%
	5	7%
Risk categories ALL		
Standard	25	34.7%
Intermediate	14	19.5%
High	30	41.7%
APML		
Standard	2	2.8%
High	1	1.3%
Treatment protocol		
BFM-09	43	59.7%
modified BFM-90	11	15.3%
ICiCLeALL-14 ver3.0	10	13.8%
APML4	3	4.2%
ALLR3	5	7%

Table 2 Characteristics Of The Febrile Neutropenia Episode In Patients

1st episode	63	87.5%
2nd or later episode	9	12.5%
Duration of fever to 1st antibiotic (in hours)	Mean: 6.16 +/- 5.4	Median: 4 (0.5-20)
Total fever duration (in hours)	Mean: 5.7+/- 3.9	Median: 4 (2-18)
Maximum fever recorded (°F)	Mean: 103+/- 0.8	Median: 103 (101.2-105.2)
Focus of infection		
Upper Respiratory Tract Infections	25	34.7%
Lower Respiratory Tract Infections	12	16.7%
Urinary Tract Infections	8	11.1%
Skin and Soft Tissue Infections	4	5.6%
Sepsis	5	6.9%
Acute Gastroenteritis	6	8.3%
Candidiasis	1	1.4%
Meningitis	2	2.7%
Acute Otitis Media	6	8.3%
Focus not identified	3	4.2%

Table 3 Laboratory Data Of Patients With Febrile Neutropenia

Hemoglobin (g%)	Mean : 8.7 +/- 1.5	Median: 8.8 (5.4-11.4)
Total Leucocyte Count (/mm^3)	Mean : 1635 +/- 975	Median: 1700 (70-5890)
Absolute Neutrophil Count (/mm^3)	Mean : 259 +/- 150	Median: 260 (0-490)
Absolute Monocyte Count (/mm^3)	Mean : 134 +/- 85	Median: 115 (10-600)
Platelet count (thousand/mm^3)	Mean : 87.9 +/- 93.7	Median: 67 (2-540)
Severe neutropenia	72	100%
Profound neutropenia	14	19.4%
Culture positive		(n=72)
Yes	30	41.7%
No	42	58.3%
Culture positivity		(n=30)
MSSA	2	6.7%
MRSA	12	40%
Pneumococcus	4	13.3%
Klebsiella	3	10%
Pseudomonas	5	16.7%
Acinetobacter	2	6.7%
E.coli	1	3.3%
Non fermenters	3	10%

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